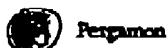


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Attachment A

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6-Chloropuines and Organostannanes in Palladium Catalyzed Cross Coupling Reactions



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6-Chloropurines and Organostannanes in Palladium Catalyzed Cross Coupling Reactions

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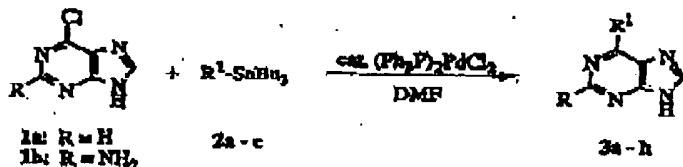
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Abstract: Carbon-carbon bond formation in the purine 6-position can easily be accomplished by palladium catalyzed cross coupling between 6-chloropurines and organostannanes without protection of the purine ring *NH* function. This technique provides a convenient route to purine cyclitides.

Kineticin (6-furfurylaminopurine) and related 6-substituted purines, called cytokinins, are known to stimulate cell growth and cell division in plants.¹ Several purines with potent cytokinin activity contain a 6-alkyl or 6-alkyl substituent.² An efficient route to these compounds would be transition metal catalyzed cross coupling of organometallic reagents with readily available 6-halopurines. For instance, 6-chloropurine **1a** (Scheme 1) is commercially available and the substance can also easily be prepared on a large scale.³ Because of the acidity of the purine ring *NH* function (*pKa* of 6-chloropurine: 7.85),⁴ organometallic reagents with low toxicity are desired. Examples of transition metal mediated couplings of purines with a free *NH* function are restricted to palladium catalyzed Heck coupling of terminal alkynes with halopurines,⁵ and nickel catalyzed coupling of methylthiopurine with Grignard reagents in which case 2.5 equivalents of the basic Grignard reagents were required.⁶ Palladium catalyzed cross coupling between heteroaryl halides and organotin derivatives is an established method for carbon-carbon bond formation in heterocycles,⁷ but the scope of this method is rarely investigated in the purine ring system.⁸ Only coupling reactions employing *N*-9 alkylated iodopurines are reported. In fact, very recently the first two examples of coupling in the purine 6-position appeared.^{9a}

Palladium catalyzed cross coupling of organostannanes **2a-c** with 6-chloropurines **1a-b** has been studied (Scheme 1, Table 1).

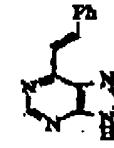
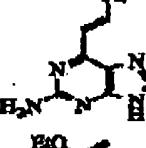
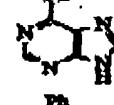
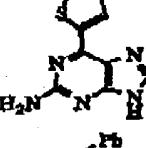
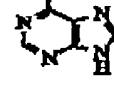


Scheme 1

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Table 1. Pd-Catalyzed Coupling between Organotinanes and Chloropurines.

Fluor. 1	Organotinane 2	Reac. time (h)	Temp. (°C)	Product 3	Yield (%)
1a	PhCH ₂ -CH ₂ SnBu ₃ 2a ¹¹	20	80		34
1b	2a	45	80		75
1a	CH ₂ =C(OBu)SnBu ₃ 2b	20	80		38
1a	PhSiBu ₃ 2c	20	100		31
1b	2c	45	100		73
1a	(2-Phenyl)SnBu ₃ 2d ¹²	20	90		51
1b	2d	45	90		76
1a	PhCH ₂ SnBu ₃ 2e ¹³	20	130		36

Organostannanes are known to tolerate a wide variety of functional groups on the coupling partners,⁹ and the purines 2a - a coupling with the relatively acidic purine 1a and 1b. Bis(triphenylphosphine)palladium(II) dichloride was found to be a suitable catalyst.¹⁰

This methodology makes purines with alkenyl-, aryl-, and heteraryl substituents in the 6-position easily accessible, and the potent cytotoxic 6-*trans*-styrylpurine 3a, was prepared in a one-step procedure superior to the methods reported earlier.¹⁴ Even the much less reactive benzyl(triethyl)stannane 2a participated in the coupling to give the 6-benzylpurine 3b in a moderate yield.

The 6-alkenyl purines 3a - b were prepared from a 1 : 9 mixture of *cis* and *trans* styryl reagent 2a (1.3 equiv.), but only the *trans* products were formed as judged by ¹H NMR of the crude products, indicating a slightly higher reactivity of the *trans* organostannane. Isomerization of the alkenes in the reaction can not be excluded, but retention of the alkenylstannanes double bond geometry is generally observed in palladium catalyzed cross couplings.⁹

The order of reactivity of aryl halides in palladium mediated cross coupling reactions is found to be Ar-I > Ar-Br >> Ar-Cl.⁹ Only aryl chlorides with an electron deficient ipso carbon will participate in the reaction. For instance, 2- and 4-chloropyridinides are shown to be sufficiently activated for the coupling to occur.⁷ In earlier reports, iodopurines have been employed in couplings with organostannanes,⁸ and even though the yields in Hock couplings of 6-chloropurines are rather moderate compared to the corresponding iodopurines,^{9,15} the present study shows that the 6-chloropurines 1a and 1b are reactive enough to give high yields of the coupling products in palladium catalyzed reactions with alkenyl- and aryltin derivatives. This is a great advantage since iodopurines are less available. In fact, iodopurines are often prepared from the corresponding chloropurines.^{15,16}

The lower reaction rate observed in the couplings of 2-amino-6-chloropurine 1b compared to 6-chloropurine 1a might be attributed to higher electron density in the former ring, making the compound less activated for nucleophilic attack from Pd(0).⁹ Initially, the coupling reactions with the 2-amino compound 1b were carried out in a much less concentrated solution due to poor solubility, but reactions of the purine 1a seem not to be significantly affected by concentration.

In summary, carbon-carbon bond formation in the purine 6-position can easily be accomplished by palladium catalyzed cross coupling of readily available 6-chloropurines with organostannanes without protection of the purine ring NH function. This technique provides an efficient route to potent cytokinines.

References and Notes.

- Miller, C. O. *Ann Ent Plaz Physiol* 1961, 12, 395-408.
- a) Henderson, T. R.; Prickett, C. R.; Leonard, N. L.; Schmidt, R. Y.; Skoog, F. *Phytochemistry* 1975, 14, 1687-1690. b) Nishikawa, S.; Kumazawa, Z.; Mizutani, H.; Kashihara, N. *Agro. Biol. Chem.* 1986, 50, 1029-1031. c) Nishikawa, S.; Kumazawa, Z.; Kashihara, N.; Mizutani, H.; Kondo, H. *Agro. Biol. Chem.* 1985, 49, 3353-3354.
- Benzon, A. G.; Robins, R. K. *J Appl. Chem.* 1962, 12, 432-437.
- Harlin, G. B.; Chapman, N. B. *J. Chem. Soc.* 1963, 3017-3022.
- Koyama, S.; Kumazawa, Z.; Kashihara, N. *Nucl. Acids Res., Symp. Ser.* 1982, 17, 41-44.
- Sugimura, H.; Takei, H. *Bull. Chem. Soc. Jpn.* 1965, 50, 664-666.
- For recent reviews, see for instance: a) Kalinic, V. N. *Synthesis* 1992, 413-432. b) Ueda, K.; Beauche, T. *Acta Chem. Scand.* 1993, 47, 102-121.
- a) Nair, V.; Turner, G. A.; Chamberlain, S. D. *J. Am. Chem. Soc.* 1987, 109, 7223-7224. b) Nair, V.; Bagger, G. S. *J. Am. Chem. Soc.* 1989, 111, 8502-8504. c) Nair, V.; Purdy, D. R.; Sella, T. B. *J. Chem. Soc., Chem. Commun.* 1989, 878-879. d) Nair, V.; Purdy, D. F. *Tetrahedron* 1991, 47, 365-382. e) Van Aartsen, A. A.; Manna, P.; Weyns, N. J.; Ikeda, S.; De Clercq, E.; Herkewij, P. A. *J. Med. Chem.* 1993, 36, 2938-2942.
- a) Sella, J. K. *Pure Appl. Chem.* 1985, 57, 1771-1780. b) Sella, J. K. *Angew. Chem.* 1986, 98, 504-519.

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10. The organostannane 2 (1.3 mmol) was added to a mixture of bis(triphenylphosphine)palladium(0) dichloride (39 mg, 0.03 mmol) and 6-chloropyruate 1a (1.0 mmol) in dry DMP (5 mL) or 2-amino-6-chloropyrimidine 1b (1.0 mmol) in DMP (15 mL) and the mixture was stirred under N₂ at the temperature indicated in Table 1, before the reaction mixture was filtered and evaporated, and the residue was washed with ether. The crude product was purified by flash chromatography or recrystallization. 3a: ¹H NMR (CDMSO-d₆) δ 6.32 (s, 3H), 7.4 - 7.5 (m, 4H), 7.7 (m, 2H), 8.10 (s, 1H), 8.25 (d, *J* 16 Hz, 1H), 12.6 (bs, 1H). MS (ELI): 237 (2, M⁺), 207 (100). 3c: ¹H NMR (CDMSO-d₆) δ 1.46 (t, *J* 7 Hz, 3H), 4.15 (s, *J* 7 Hz, 2H), 4.77 (d, *J* 2 Hz, 1H), 5.68 (d, *J* 2 Hz, 1H), 8.77 (s, 1H), 8.91 (s, 1H), 13.6 (bs, 1H). MS (ELI): 190 (100, M⁺). 3m: ¹H NMR (CDMSO-d₆) δ 6.38 (s, 2H), 7.5 - 7.6 (m, 3H), 8.11 (s, 1H), 8.7 - 8.8 (m, 2H), 12.7 (bs, 1H). MS (ELI): 211 (100, M⁺). 3f: ¹H NMR (CDMSO-d₆) δ 7.36 (m, 1H), 7.92 (m, 1H), 8.66 (m, 2H), 8.84 (s, 1H), 13.7 (bs, 1H). MS (ELI): 202 (100, M⁺). 3g: ¹H NMR (CDMSO-d₆) δ 6.40 (s, 2H), 7.28 (m, 1H), 7.30 (m, 1H), 8.12 (s, 1H), 8.57 (m, 1H), 12.7 (bs, 1H). MS (ELI): 217 (100, M⁺).
 11. Lahadia, J. W.; Sille, J. K. *J. Am. Chem. Soc.* 1963, 85, 6129-6137.
 12. Pinhey, J. T.; Roche, E. G. *J. Chem. Soc., Perkin Trans. 1* 1968, 2415-2421.
 13. Devine, A. G.; Roberts, B. P.; Smith, J. M. *J. Chem. Soc., Perkin Trans. 2* 1972, 2221-2224.
 14. a) Hampton, A. *J. Heterocyclic Chem.* 1974, 11, 255-256. b) Taylor, E. C.; Martin, S. H. *J. Am. Chem. Soc.* 1974, 96, 8095-8102.
 15. Tanji, K. I.; Higashino, T. *Chem. Pharm. Bull.* 1968, 16, 1939-1941.
 16. a) Elina, G. B.; Hinchliffe, G. H. *J. Am. Chem. Soc.* 1956 78, 3508-3510. b) McKenzie, T. C.; Sprain, J. W. *J. Org. Chem.* 1962, 27, 4881-4884.

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